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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,482	09/23/2003	Claudio Cavazza	4865-62	9079

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EXAMINER
KIM, JENNIFER M

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,482	CAVAZZA, CLAUDIO	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-35* is/are pending in the application.

4a) Of the above claim(s) *17-22,25-30 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16, 23, 24, 31, 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Lithium as a specie of a nephrotoxic or potential nephrotoxic external agent is acknowledged. The traversal is on the ground(s) that the various species identified by the Examiner have different chemical origins, but all of them have the same technical feature in the frame of the present invention that they all cause nephrotoxicity. This is not found persuasive because the fact that these compounds have different chemical origins, they have different known therapeutic effects involving unrelated biological pathway. Therefore they do not relate to a single general inventive concept. Therefore, the species requirement made on the previous Office Action is deemed proper and made final.

Accordingly, claims 9-16, 23, 24, 31 are being examined and claims 17-22, 25-30 and 33-35 are withdrawn from consideration since they are non-elected invention.

Action Summary

The rejection of claims 9-14 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,653,349B1 is hereby expressly **withdrawn** in view of Applicants' filing of terminal disclaimer.

The rejection of claims 9-11 under 35 U.S.C. 112, first paragraph (enablement) is being **maintained** for the reasons stated in the previous Office Action. However, the rejection is modified in this Office Action to include newly added claims.

The rejection of claims 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424) is being **maintained** for the reasons stated in the previous Office Action because the claims are not limited to the elected specie.

In view of the amendment and Applicants' election of species, additional rejection as been made in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 9-16, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treating a kidney dysfunction", does not reasonably provide enablement for the "preventing a kidney dysfunction". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

2. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for preventing a kidney dysfunction or preventing nephropathy caused by a nephrotoxic agent which comprises administering to an individual in need thereof 2-5mg of acetyl L-carnitine and 2-5mg of propionyl L-carnitine/kg body weight/day or an equimolar amount of a pharmacologically acceptable salt thereof. The nature of the invention is extremely complex in that it encompasses the actual prevention of a kidney dysfunction disorder (i.e. nephropathy) such that the subject treated with above compounds does not contract a kidney dysfunction.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass prevention of a complex kidney disorder in humans, which has potentially many different causes (i.e. many different nephrotoxic agents or combination of agents. Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually prevent a kidney dysfunction is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of s kidney dysfunction.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of a kidney dysfunction.

State of the Art: While the state of the art is relatively high with regard to treatment of kidney dysfunction (i.e. nephropathy), the state of the art with regard to prevention of such dysfunction is underdeveloped. The state of the art, Suzuki et al. (U.S.Patent No. 5,246,835) report that it is difficult to cure nephropathy of a patient and that nephropathy generally develops into terminal renal insufficiency within 5 or 6 years. (column 1, lines 20-25).

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual prevention of a kidney dysfunction in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of a kidney dysfunction.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine

whether or not the combination is effective for prevention of kidney dysfunction. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to prevention of a kidney dysfunction with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of kidney dysfunction with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of kidney dysfunction in a subject by administration of one of the claimed compounds.

Therefore, a method of preventing a kidney dysfunction caused by a nephrotoxic or potential nephrotoxic external agent which comprises administering to an individual in need thereof 2-5mg of acetyl L-carnitine and 2-5mg of propionyl L-carnitine/kg body weight/day or an equimolar amount of a pharmacologically acceptable salt thereof is not considered to be enabled by the instant specification.

Claims 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "an individual at risk to be contaminated by lithium" lacks literal support in the specification as originally filed.

This is a New Matter rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "an individual at risk to be contaminated by lithium" renders the claim indefinite because it is not clear how one would determine when one is at risk to be contaminated by lithium. Everyone is somewhat at a risk to be contaminated by lithium because there are significant amounts of lithium in many soils. Therefore, one of ordinary skill in the art would not be able to determine specific subject population intended.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424).

Calvani et al. teach the pharmaceutical composition comprising L-carnitine or an alkanoyl L-carnitine or a pharmacologically acceptable salts thereof, useful as a medicament for inhibiting nephrotoxicity resulting from the administration of an immunosuppressant drug such as cyclosporine-A, tacrolimus, rapamycin and deoxyspergualine. (abstract). Calvani et al. illustrate tests showing carnitine-induced renal protection with administration of **acetyl L-carnitine** or **propionyl L-carnitine**. (see Experimental tests, column 3-6). Calvani et al. teach the effective amount of L-carnitine in two different doses of 2mg/l and 5mg/l.

Calvani et al. do not expressly teach the composition comprising acetyl L-carnitine and propionyl L-carnitine in a single formulation for inhibiting nephrotoxicity.

It would have been obvious to one of ordinary skill in the art to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation for inhibiting nephrotoxicity because Calvani et al. teach that each of the active agents are effective for the such inhibition. One of ordinary skill in the art would have been motivated to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation in order to achieve an expected additive benefit of inhibiting nephrotoxicity as illustrated by Calvani et al. One of ordinary skill in the art would have been reasonably expect that the obvious method would provide kidney protection from a kidney dysfunction/nephropathy caused by nephrotoxic agent (cyclosporine, tacrolimus, rapamycin) because each of the active agents has a renal protective effect as demonstrated by Calvani et al.

Claims 9-16, 23-24, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calvani et al. (U.S. Patent No. 5,955,424) of record in view of Walker et al. (1982).

Calvani et al. teach the pharmaceutical composition comprising L-carnitine or an alkanoyl L-carnitine or a pharmacologically acceptable salts thereof, useful as a medicament for inhibiting nephrotoxicity resulting from the administration of an immunosuppressant drug such as cyclosporine-A, tacrolimus, rapamycin and deoxyspergualine. (abstract). Calvani et al. illustrate tests showing carnitine-induced renal protection with administration of **acetyl L-carnitine** or **propionyl L-carnitine**. (see Experimental tests, column 3-6). Calvani et al. teach the effective amount of L-carnitine in two different doses of 2mg/l and 5mg/l. Calvani et al. teach that **acetyl L-**

carnitine or **propionyl L-carnitine** is effective for treating renal toxicity of **tubular lesion** induced by cyclosporin A. (column 4, lines 38-43).

Calvani et al. do not expressly teach the composition comprising acetyl L-carnitine and propionyl L-carnitine in a single formulation for inhibiting nephrotoxicity caused by Lithium.

Walker et al. teach that lithium therapy is associated with tubular lesion as a nephrotoxicity. (abstract).

It would have been obvious to one of ordinary skill in the art to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation for treating tubular lesion in nephrotoxicity caused by lithium because Calvani et al. teach that each of the active agents are effective for the nephrotoxic related tubular lesion caused by cyclosporin-A and because Walker et al. teach that lithium also causes tubular lesion as nephrotoxicity. One of ordinary skill in the art would have been motivated to combine acetyl L-carnitine and propionyl L-carnitine in a single formulation in order to achieve an expected additive benefit of inhibiting tubular lesion of nephrotoxicity due to lithium. One of ordinary skill in the art would have been reasonably expect that the obvious method would provide kidney protection from a kidney dysfunction/nephropathy caused by nephrotoxic agent (lithium) because each of the active agents has a renal protective effect of treating the same nephrotoxic condition e.g. tubular lesion caused by cyclosporine-A. There is a reasonable expectation of successfully treating nephrotoxicity caused by lithium, i.e. tubular lesion because Calvani et al. specifically

teaches that the each of active agents are useful for treating tubular lesion that is specific condition of nephrotoxicity.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

Applicant arguments filed August 16, 2007 have been fully considered but they are not persuasive. Applicant essentially argues that instant specification provides enablement for "preventing a kidney dysfunction" because the protective activity against renal insufficiency "crush syndrome" was tested by administering acetyl L-carnitine and propionyl L-carnitine three days preceding the test showing the preventive effect of the invention. This is not found persuasive because the vivo experimental working example report that there is a surprising marked "reduction" with the instant combination but there is no indication that there is an absolute "prevention" as claimed. Applicant argues that the state of the art Suzuki et al. refers to the clinical diagnosis of diabetic nephropathy characterized by continuous proteinuria is not a nephrotoxic agent and will know that it is different from tubular-interstitial nephropathy and tubular necrosis due to

toxic agents. This is not found persuasive because Suzuki et al. teach the treatment of nephropathy that generally develops in to terminal renal insufficiency is difficult to cure. Therefore, to the extent that the claims are drawn to "prevention" of nephropathy or renal toxicity including renal insufficiency is highly speculative. More experimental data is necessary to prove that the combination would completely prevent such conditions that are difficult to cure. Therefore, a method of preventing a kidney dysfunction caused by a nephrotoxic or potential nephrotoxic external agent which comprises administering to an individual in need thereof 2-5mg of acetyl L-carnitine and 2-5mg of propionyl L-carnitine/kg body weight/day or an equimolar amount of a pharmacologically acceptable salt thereof is not considered to be enabled by the instant specification. Applicant argues that no indication is given by Calvani et al. on the capability of the combination of acetyl L-carnitine and propionyl L-carnitine of protecting the kidney from several toxic agents. This is not found persuasive because Calvani et al. provide every indication that these two agents would protect the specific nephrotoxic condition such as tubular lesion cause by a nephrotoxic agent (e.g. lithium) because each of the active agents were taught to be effective for the treatment of the same condition caused by cyclosporin A. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Kim
Primary Examiner
Art Unit 1617

Jmk
October 24, 2007